## *Remarks*

Claims 43 and 47 have been amended to depend from claim 1 and to incorporate the limitations of the claims from which these claims previously depended. Claim 121 and 125 have been amended to depend from claim 82 and to incorporate the limitations of the claims from which these claims previously depended. Claim 66 has been amended to correct a typographical error such that the claim now recites "0.1 mg/ml" instead of "0.01 mg/ml." Claim 83 has been amended to recite that the chelating agent and the tonicifer are in at a concentration no greater than about 10 mM and no greater than about 150 mM, respectively. Claims 73 and 147 have been amended to recite "wherein said mixture consists of 0.18% methyl paraben and 0.02% propyl paraben." Support for these amendments can be found throughout the specification as filed. Accordingly, no new matter has been introduced and entry of this amendment is respectfully solicited. Claims 1-7, 9-33, 36-66, 71-155 are pending.

Applicants thank the Examiner for clarifying the record regarding the Notice of Allowance mailed by the Office on September 30, 2002, its return to the Office, and subsequent failure of the Office to remail the papers. Applicants also thank the Examiner for reopening prosecution in light of this error. However, Applicants note that the Examiner has provided no authority for the position that the mailing of the Notice of Allowance was without effect due to the return of the papers and the Office's subsequent failure to re-mail said papers. Thus, Applicants request that the Examiner verify that the Notice of Allowance mailed on September 20, 2002 remains a part of the written record of the instant application or provide the authority to support the Office's expungement of such a paper.

## I. Oath/Declaration

The Examiner has required a supplemental oath or declaration in conjunction with a response to the instant Official Action because "[a]s a result of amendment(s) to the claim(s), the pending claims no longer substantially embrace the invention as set forth in the statement of the invention and/or in the original claims." *See*, Paper No. 21, page 3, first paragraph.

Applicants respectfully disagree, and traverse this objection. Preliminarily, Applicants are confused as to which of the pending claims do not allegedly embrace the invention as set forth in the statement of the invention and/or the original claims. Applicants note that the pending claims are directed to liquid and lyophilized formulations of a specific deletion mutant of KGF-2, Ser (69) to Ser (208) of SEQ ID NO:2 or KGF-2 Δ33. The formulations encompassed by the pending claims are specifically contemplated in the "Summary of the Invention" of the specification. *See*, specification, *e.g.*, page 3, line 1 to page 4, line 24. Moreover, the subject matter in the pending claims was also encompassed by the original claims filed with the application as of its earliest priority date. *See, e.g.,* original claims, in particular, original claims 1, 8, and 20. Thus, Applicants assert that the subject matter encompassed by the currently pending claims is indeed embraced by the statement of the invention and the original claims of the instant application. Accordingly, Applicants maintain that a supplemental oath or declaration is not required. Should the Examiner disagree, Applicants respectfully request that the Examiner identify, with particularity, the subject matter alleged to be outside the scope of the statement of the invention and the original claims.

## II. Objections to the Specification

The Examiner has objected to the specification for allegedly improperly incorporating documents by reference into the specification. In particular, the Examiner alleges that "the specification does not state with specificity why these documents are being incorporated and does not specifically indicate where that specific material is found in the various documents." *See*, Paper No. 21, page 4, first paragraph.

Applicants respectfully disagree and traverse this objection.

Preliminarily, Applicants note that the Examiner has previously raised a similar objection in the Official Action mailed February 14, 2002 (Paper No. 7). This objection has presumably been overcome and the claims of the invention were held to be allowable, as evidenced by the fact that a Notice of Allowance was prepared and mailed by the Office on September 30, 2002. Thus, Applicants are confused as to why the instant objection for improper incorporation by reference is being reiterated by the Examiner.

Regardless of the propriety of the instant objection, Applicants assert that the instant specification has properly incorporated the objected documents into the specification as outlined by the M.P.E.P. and the case law.

M.P.E.P. § 608.01(p)(I)(A) clearly sets forth the criteria for incorporating material into the specification by reference. The M.P.E.P. makes a distinction between the incorporation by reference of "essential" versus "non-essential" material. "Essential" material, or material that is necessary to satisfy § 112 requirements, may only be incorporated by reference into a specification from a U.S. patent, a U.S. patent application publication, or a pending U.S. application. Essential material may not be incorporated by reference from foreign patents or applications and/or non-patent applications. *See*, §608.01(p)(I)(A) at 600-79. Conversely, "non-essential" material, or material that provides a background of the invention or describes the state of the art, may be incorporated by reference not only from U.S. patents, patent application publications, or pending applications, but also from foreign patents or applications and/or non-patent applications. *See*, §608.01(p)(I)(A) at 600-79.

As previously noted in the response to the Patent Office, filed July 10, 2002, Applicants assert that the incorporation by reference of the instant specification constitutes non-essential matter in that the references being incorporated provide description of proteins and information known in the art that is not encompassed by the pending claims. Thus, Applicants contend that the specification has properly incorporated by reference the objected documents. To the extent that the Examiner contends that some material is "essential", Applicants ask that the Examiner identify this essential matter so that Applicants may incorporate that material directly into the specification, as per M.P.E.P. § 608.01(p)(I)(A)(2).

In addition, the Examiner relies on case law in support of his objection by citing a passage from *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679 summarizing the Federal Circuit's interpretation of the criteria necessary for a proper incorporation by reference. In particular, the Examiner emphasizes the court's holding in *In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973)) that a statement clearly identifying the subject matter which is to be incorporated and

where it can be found is necessary for the proper incorporation by reference of material "for economy, amplification, or clarity of exposition." *Seversky*, 474 F.2d at 674.

Contrary to the Examiner's objection, the specification indeed satisfies the standard for incorporation by reference set forth in *Seversky* by clearly providing such statements identifying the subject matter to be incorporated. For example, on page 17, the specification points the skilled artisan to additional information on other non-claimed compounds that were known in the art to be useful in gel formulations for wound healing. Similarly, in the other instances where the specification incorporates expository information, the specification also provides a clear indication of the contents of that information. Moreover, the specification clearly states that the entire disclosure of the objected documents have been incorporated by reference. Thus, this statement provides the necessary location, *e.g.*, the entire document, of the subject matter being incorporated.

Moreover, Applicants assert that the Examiner's further emphasis on the holding in *In re Lund* is improper in the instant application. Applicants note that the statement from *Lund* relied upon in *Advanced Display Systems* was set forth to address the issue of relying on information from a parental application by only making a benefit claim connection between the parent and child applications. *See*, *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). However, the incorporation by reference of the instant application is distinguishable from *Lund*, in that the instant objection does not encompass an incorporation of a reference merely through a priority claim. Rather, the Examiner's objection is directed to the proper incorporation by reference of expository information into the specification. Thus, Applicants contend that *Lund* is inapplicable to the instant objection.

Based on the totality of the evidence, as discussed above, Applicants contend that the instant specification has properly incorporated non-essential material by reference into the specification and has made clear statements as to the nature of the information being obtained from the incorporated reference and its location in the reference. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection for an alleged improper incorporation by reference.

## III. Objections to the Claims

The Examiner has objected to claims 43, 47, 66, 83, 121, and 125 under 37 C.F.R. § 1.75(c) as being improper dependent claims for allegedly failing to limit the subject matter of the previous claim from which it depends.

**a.** In particular, the Examiner has alleged that claims 43, 47, 121, and 125 effectively broaden the scope of the claims 40 and 118, in that claims 40 and 118 require a thickening agent whereas claims 43, 47, 121, and 125 allegedly encompass formulation where no thickening agent is present. *See*, Paper No. 21, page 4, paragraph 7a.

Applicants respectfully disagree. However, Applicants have amended the dependencies of claims 43, 47, 121, and 125 such that they now depend from either claim 1 or claim 82 and incorporate all of the limitations of the claims from which they previously depended, thereby obviating the Examiner's objection. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objections to claims 43, 47, 121, and 125.

**b.** The Examiner has also objected to claim 66 for allegedly broadening the lower limit of the range of the polypeptide as claimed in claim 1. See, Paper No. 21, page 4, paragraph 7a.

Applicants note that the phrase "about 0.01 mg/ml" was a typographical error. Applicants thank the Examiner for pointing out this error. Accordingly, Applicants have amended claim 66 to correct the typographical and to recite "about 0.1 mg/ml." Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection of claim 66.

**c.** The Examiner has further objected to claim 83 for allegedly broadening claim 82 in that claim 83 allegedly "encompasses values of where neither a chelating agent" nor a "tonicifier" is added." See, Paper No. 21, page 5, paragraph 7c.

Applicants respectfully disagree. However, Applicants have amended claim 83 to recite that the chelating agent and tonicifer are at a concentration no greater than about 10 mM and no greater than about 150 mM, respectively. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection to claim 83.

## IV. Written Description Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-7, 9-33, 36-66, 71-73, and 82-150 under 35 U.S.C. §112, first paragraph for alleged lack of written description. *See*, Paper No. 21, paragraph 8.

**a(1).** The Examiner alleges that claims 1-7, 9-33, 35-66, 71-73, and 82-146 lack written description based an isolated passage on page 8 of the specification that teaches preferred embodiments of the invention containing specific preservatives at specified concentrations. In particular, the Examiner asserts that

> The specification has not been found to provide an adequate written description of whether other preservatives, or where preservatives are to be used outside of the disclosed ranges. Accordingly, the specification does not provide an adequate written description of using any preservative, or specific preservatives at any concentration.

*See*, Paper No. 21, page 6, paragraphs 10-12.

Applicants respectfully disagree and traverse this rejection

The Federal Circuit has re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed,'" *Union Oil Company of California v. Atlantic Richfield Company*, 208 F.3d 989, 54 U.S.PQ.2d 1227 (Fed. Cir. 2000); *In re Smith*, 481 F.2d910, 178 USPQ 620 (CCAP 1973) (holding that the claimed subject matter need not be described in *haec verba* to satisfy the description requirement.) Further, the Federal Circuit has emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification; and not whether the specific embodiments had been explicitly described or exemplified. Indeed, the court noted that "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Union Oil Company of California v. Atlantic Richfield Company*, 208 F.3d at 1001, (emphasis added).

Applicants submit that, as a threshold matter, claim 1 does not encompass the use of any preservative. Rather, claim 1 is limited to a preservative selected from the group consisting of "m-cresol, chlorobutanol, and a mixture of methyl paraben and propyl paraben." The specification clearly and specifically describes the use of any of these

preservatives in the instant invention. *See, e.g.,* specification, at page 4, lines 17-19. Moreover, contrary to the Examiner's assertions, the specification as a whole indeed envisions and describes the use of preservatives at any concentration. For example, the specification contemplates on page 4, lines 17-19, the addition of a preservative with no limitation on the concentration. In addition, the specification teaches in Example 10, page 66, how to determine what concentration to use, namely basing that determination on "literature values as well as FDA/USP and BP guidelines." *See, e.g.,* page 66, lines 16-17. Thus, Applicants assert that although the specification lists the contemplated preservatives of claim 1 at preferred concentrations, the skilled artisan, upon reading the specification, would understand that the invention also encompassed the preservatives at concentrations other than the preferred embodiments.

In addition, Applicants submit that the underlying basis of the Examiner's argument is to limit the instant invention to the preferred embodiments described in the specification by asserting that the specification does not teach the broader scope of the claims. Even assuming, *arguendo*, that the specification only taught a narrow invention (which is not the case in the instant application), this reasoning does not comport with the law. It is a well-settled principle that a specification may adequately describe a broadly claimed invention without describing all species that the claim encompasses. *See, Utter v. Hiraga*, 845 F.2d 993, 6 U.S.P.Q.2d (BNA) 1709 (Fed. Cir. 1988). As the court noted in *In re Smythe* 480 F.2d 1376, 1382, 178 U.S.P.Q. (BNA) 279 (Fed. Cir. 1973), "we cannot agree with the broad proposition... that in every case where the description of the invention in the specification is narrower than that in the claim there has been a failure to fulfill the description requirement in section 112." Moreover, although the claims must be construed in light of the specification, any limitations from the specification are not to be read into the claims. *See, Golight, Inc. v. Wal-Mart Stores*, No. 02-1608 (Fed. Cir, Jan. 20, 2004). Indeed, the court held that

> if everything in the specification were required to be read into the claims, or if structural claims were to be limited to devices operated precisely as a specification-described embodiment is operated, there would be no need for claims.

*SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985).

Moreover, the court has further held that the claims of an invention are not necessarily limited to the preferred embodiments disclosed in the application, even when only one embodiment is disclosed. Without a specific disclaimer of the subject matter, disclosure of preferred embodiments can not limit the scope of the claims. *Golight v. Wal-Mart*, No. 02-1608, citing *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1301 (Fed. Cir. 2003).

Thus, based on the applicable case law, Applicants contend that the Examiner's rejection based on written description provided by preferred embodiments is improper. Moreover, as discussed above, Applicants further contend that the specification does indeed contemplate and describe not only the preferred embodiments cited by the Examiner, but also the scope of the subject matter encompassed by the rejected claims. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-7, 9-33, 35-66, 71-73, and 82-146 under 35 U.S.C. § 112, first paragraph for lack of written description.

**a(2).** The Examiner has rejected claims 73 and 147 for alleged lack of written description. In particular, the Examiner alleges that claims 73 and 147 allow for the inclusion of other preservatives at any concentration. *See*, Paper No. 21, page 6, paragraph 13.

Applicants respectfully disagree and traverse this rejection. For the reasons stated above, the specification indeed has written description for the use of a broad range of preservatives in the composition of the present invention. However, Applicants have amended claims 73 and 147 to recite "wherein said mixture consists of 0.18% methyl paraben and 0.02% propyl paraben." Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 73 and 147 under 35 U.S.C. § 112, first paragraph for lack of written description.

**b.** Similar to the Examiner's rejection described in section IV(a)(1) of the instant response, the Examiner has also alleges that claims 21-24, 27-33, 36-39, 54, 56, 101-104, and 116 lack written description based on an isolated passage of the specification, *e.g.*, page 12, lines 12-21, that teaches preferred embodiments of the invention containing specific bulking agents at specified concentrations. In particular, the Examiner contends that the specification does not "provide adequate written

description of other 'bulking agents,' nor has the specification been found to provide alternative concentrations at which said bulking agents are to be used." *See*, Paper No. 21, page 7, paragraph 15.

Applicants respectfully disagree and traverse this rejection.

Applicants reassert that it appears that the underlying basis of the Examiner's argument is to limit the instant invention to the preferred embodiments described in the specification by asserting that the specification does not teach the broader scope of the claims. As discussed above, it improper to limit the scope of the claims to the preferred embodiments disclosed in the specification.

In addition, Applicants note that the disclosure of the instant specification as a whole clearly contemplates more than the preferred bulking agents relied on by the Examiner. For example, the specification clearly describes at page 3, lines 19-21 a formulation "comprising a KGF-2 polypeptide, a lyophilization bulking agent and a buffering agent having a buffering capacity of between about pH 5.0 and about pH 8.0." This language clearly contemplates additional bulking agents to those that are disclosed on page 12, lines 12-21. In addition, the specification describes additional examples of bulking agents at a broad range of concentrations. *See, e.g.,* specification, at page 13, line 3. Moreover, the original claims of the specification provide further written description for the broad class of bulking agents at concentrations outside of those disclosed as preferred embodiments. For example, original claim 21 describes a formulation of the invention "further comprising a bulking agent." *See, e.g.,* original claims, at page 74. Thus, the specification clearly provides an adequate written description of the subject matter of a bulking agent as encompassed by the claims at issue.

The Examiner further contends that the statement in the specification that "other pharmaceutically acceptable bulking agents are included in the formulation" does not provide adequate written description of the claimed invention. In particular, the Examiner alleges that "applicant is attempting to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, through obviousness." *See*, Paper No. 21, page 7, paragraph 15.

However, Applicants disagree. Preliminarily, Applicants are confused as to the basis of the Examiner's reasoning. Obviousness is a separate issue with a separate legal

standard and is inapplicable to the issue to hand. Applicants respectfully request clarification of this rejection.

Regardless of the Examiner's basis for this portion of the rejection, Applicants contend that the statement that "other pharmaceutically acceptable bulking agents are included in the formulation" indeed provides adequate written description for the claimed invention. It is a well-established principle that a specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). If a term is one that is readily known in the art, all that is required is to describe the invention such that one of ordinary skill in the art would immediately envision the product claimed. Applicants contend that the term "bulking agent" was well-known in the chemical arts at the time of filing. *See*, e.g., Nema *et al.*, "Excipients and their use in injectable products," *PDA J. Pharm. Sci. & Tech.* 51(4):166-171 at Table VII, page 169 (submitted herewith as Reference AR32). Thus, Applicants contend that a skilled artisan, upon reading the specification, would readily envision the claimed subject matter of a "bulking agent" as encompassed by the claimed invention.

In view of the foregoing arguments, Applicants contend that the specification clearly satisfies the written description requirement for the claimed "bulking agents" of the present invention. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 21-24, 27-33, 36-39, 54, 56, 101-104, and 116 under 35 U.S.C. § 112, first paragraph for lack of written description.

**c.** The Examiner further rejects claims 43 and 121 under 35 U.S.C. § 112, first paragraph for allegedly introducing new matter. In particular, the Examiner alleges that the specification does not provide written description for a thickening agent which is present "in a concentration of 0 to 5% (w/v). *See*, Paper No. 21, page 7, paragraph 16.

Applicants respectfully disagree and traverse this rejection.

Applicants note that as the Examiner has pointed out, page 16 discloses a range of about 0% to about 5% in reference to the presence of sucrose. However, the specification also explicitly discloses a thickening agent, which is present in a concentration of 0 to 5% (w/v). *See, e.g.,* specification, at page 15, lines 14-15. Thus, the specification clearly describes the subject matter encompassed by claims 43 and 121. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 43 and 121 under 35 U.S.C. § 112, first paragraph for lack of written description.

**d.** The Examiner also rejects claims 148-150 for alleged lack of written description. In particular, the Examiner cites an isolated passage of the specification at page 6 that discusses particular properties of KGF-2 polypeptides at particular ranges of pH. The Examiner then relies on this passage and alleges that

> [i]n view of such cautionary teachings in the disclosure, the specification has not been found to provide an adequate written description of pharmaceutical compositions comprising said KGF-2 polypeptides where the pH is outside of this disclosed range. Accordingly, the specification does not reasonably suggest that applicant was in possession of the claimed invention at the time of filing.

*See*, Paper No. 21, page 8, paragraphs 18-19.

Applicants respectfully disagree and traverse this rejection.

The Federal Circuit has held that a written description may not limit the scope of the claims unless the applicant redefines a term such as to clearly deviate from the ordinary and customary meaning or clearly disavows scope of the claims. *Golight v. Wal-Mart*, No. 02-1608, citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002).

Neither of these criteria is present in the instant application. First, the specification does not deviate from using the term "pH" in any way that is contrary from the ordinary and customary meaning in the art. The specification clearly uses the term "pH" to describe the alkalinity/acidity of the composition. Second, Applicants have in no way disavowed compositions of the claimed invention that are at a pH of 4.5 or less or at a pH above 8.0. Applicants note that although the specification cautions "these polypeptides present a difficult challenge when attempting to formulate them for therapeutic uses," nowhere in the specification does it state that formulations outside of the preferred ranges of pH disclosed in the paragraph on page 6 are inoperative. The

specification merely teaches that these formulations may be more difficult than others in the pH range disclosed. Thus, the difficulty of formulating polypeptides at the outer edges of a range should not be construed as a disavowal of nor should it preclude Applicants from claiming subject matter that falls within those outer ranges.

Moreover, even if certain formulations at the outer edges of the pH range were found to be inoperative, the presence of inoperative embodiments does not preclude the specification from satisfying the requirements of § 112. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569; 224 U.S.P.Q. (BNA) 409 (holding that "it is not the function of the claims to specifically exclude... possible inoperative substances.") However, as stated above, the specification provides no evidence that these embodiments are inoperative, just that they are "difficult to formulate". The Examiner has not provided any evidence as to the inoperativeness of the embodiments at the outer edges of the pH range.

Thus, the record as whole provides no evidence that suggest that one of skill in the art would find that Applicants were not in possession of the invention encompassed by claims 148-150 at the time of filing. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 148-150 under 35 U.S.C. § 112, first paragraph for lack of written description.

## V. Enablement Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 43 and 121 under 112, first paragraph for alleged lack of enablement. In particular, the Examiner alleges that

> [a] review of the specification fails to locate a reproducible procedure whereby the claimed pharmaceutical composition and be made and used whereby one satisfies the presence of a thickening agent yet at the same time no such thickening agent is present.

*See*, Paper No. 21, page 10, paragraph 22.

Applicants respectfully disagree and assert that the claims at issue are enabled by the specification as filed. Moreover, claims 43 and 121 have been amended to depend from claim 1 and 82, respectively. Thus, contrary to the Examiner's argument and for the reasons set forth below, Applicants contend that the pending claims are fully enabled by the specification as filed.

Applicants contend that the specification clearly sets forth how to make and use the invention as encompassed in claims 43 and 121. For example, the specification discloses that the formulations of the invention may also include a thickening agent. See, e.g., specification, at page 4, lines 8-12; and at page 15, line 3 to page 16, line 28. In addition, the specification describes how the thickening agent may be in a concentration range of 0 to 5% (w/w) and describes examples of thickening agents that may be used in the compositions of the invention. *See, e.g.,* specification, at page 15, line 14 to page 16, line 28. The specification further describes how to make a particular example of a thickened formulation, *e.g.,* at Example 3, page 59, lines 12-27. Thus, Applicants contend that the specification provides a more than adequate disclosure to enable a skilled artisan to make and use the invention encompassed by pending claims 43 and 121. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 43 and 121 under 35 U.S.C. § 112, first paragraph for lack of enablement.

## VI. Obviousness Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 1-3, 5-17, 20-32, 36, 37, 71-73, 76, 80, 82-97, 100-115, 144-147 and 151-153 under 35 U.S.C. § 103 for allegedly being obvious over Human Genome Sciences (WO 96/25422; "HGS") in view of Chen et al., (Journal of Pharmaceutical Sciences, Vol. 85, No. 4, April 1996; "Chen") and Prestreleski et al. (U.S. Patent 5,580,856, "the '856 patent"). *See*, Paper No. 21, page 11, paragraph 27.

In particular, the Examiner contends that HGS discloses KGF-2, fragments thereof and pharmaceutical compositions. The Examiner further contends the compositions disclosed in HGS can comprise "saline dextrose, water, glycerol, ethanol, and combinations thereof." Although the Examiner acknowledges that HGS does not disclose specific amino acids of the fragments of KGF-2, the Examiner asserts that HGS teaches the KGF-2 sequence and directs the artisan to use fragments of KGF-2. The Examiner further relies on the disclosure of Chen, which discloses four buffers at specific concentration ranges, to allege that the claimed concentration range of the KGF-2 polypeptide and the buffer, as well as the type of buffer, are rendered obvious. *See*, Paper No. 21, page 11, paragraphs 28-30.

The Examiner also combines HGS with the '856 patent. The Examiner contends that the '856 patent teaches formulations of KGF that contain a buffer, including citrate, at a pH range of 1 to 13 and additives or preservatives such as methyl paraben, propyl paraben or chlorobutanol. The Examiner further alleges that the '856 teaches other elements of the instant invention including osmolytes or tonicifiers such as glycine, lysine, trehalose, or sucrose; sodium citrate; and chelators such as EDTA. In addition, the Examiner contends that the '856 patent teaches a polypeptide "generally within the range of about 0.05 to about 20,000 micrograms/milliliter." The Examiner concludes that

> [w]hile the prior art may not explicitly teach certain preferred concentrations of components of the claimed compositions, or the degree to which a composition is lyophilized, such concentrations of dryness, in the absence of evidence to the contrary, are considered obvious through routine experimentation.

*See*, Paper No. 21, page 12, paragraphs 31-35.

Applicants respectfully disagree and traverse this rejection.

To establish a prima facie case of obviousness, the references alone or in combination must teach each and every element of the claimed invention. In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to come to the claimed invention with a reasonable expectation of success. *See*, M.P.E.P. § 706.02(j). Moreover, M.P.E.P. § 2143.01 instructs that some objective reason to combine the teachings of references is required when the references individually teach all aspects of the claimed invention. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Applicants contend that there is no such indication in the references provided by the Examiner, either alone or in combination, that suggests the desirability of the specific combinations claimed in the instant invention.

The first reference applied by the Examiner, HGS, does disclose the sequence of the parent KGF-2 polypeptide and fragments thereof. In addition, HGS does teach that the polypeptides of the invention, including fragments, can be used in a pharmaceutical composition. However, HGS does not teach or suggest all of the other requirements of the claims, namely that the pharmaceutical composition comprises a preservative selected from

the group consisting m-cresol, chlorobutanol, and a mixture of methyl paraben and propyl paraben.

Nor does the second reference, Chen, teach or suggest the specific combination claimed by the instant invention. Although Chen discloses using KGF at a concentration of 0.5 mg/ml to test thermal denaturation in the presence of osmolytes and salts, including sodium phosphate, ammonium sulfate, sodium citrate, and sodium chloride, Chen does not teach or suggest using the KGF polypeptide with a buffer, a pharmaceutically acceptable diluent, and a preservative as claimed by the instant invention. In addition, Applicants further contend that contrary to the Examiner's arguments, Chen actually teaches away from the concentration range of the buffers encompassed by the instant claims. Chen teaches that the addition of additives at a concentration range of 0.2 M to 3 M decreases thermal unfolding of KGF. In fact, the results of Chen's experiments suggest that higher concentrations of additives are more effective than lower concentrations. *See*, Table 1, page 420. Not only are the effective concentration used in Chen's experiments well outside of the ranges encompassed by the instant claims, the fact that high concentrations of additive were more effective teaches away from using the concentrations of additives claimed in the instant application. Moreover, there is nothing in Chen to link it to the third reference relied upon by the Examiner, the '856 patent.

It is a well-settled principle that in cases where the claimed ranges are encompassed in the ranges disclosed in the art or in those cases where mere optimization of the prior art occurred to reach the claimed ranges, those claimed ranges are deemed prima facie obvious. *See*, M.P.E.P. § 2144.05(I) and (II)(A); *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (CCPA 1976); *Merck & Co. v. Biocraft Labs., Inc.* 874 F.2d 804, 10 U.S.P.Q.2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989). However, the Federal Circuit has held that "we decline to extract from *Merck* the rule that ... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it." *In re Jones*, 958 F.2d 347, 350 21 U.S.P.Q.2d (BNA) 1941, 1943 (Fed. Cir. 1992). The court held that there must be some motivation to seek out and acquire the claimed species from the vastly broad genus without undue experimentation. *Id*, 958 F.2d at 351.

Applicants contend that the '856 patent as a whole discloses a broad genus with composition comprising an infinite number of combinations of the elements disclosed. For example, the '856 patent discloses a formulation comprising admixing a dried protein with at least one "reconstitution stabilizer" for the purpose of reducing aggregation upon reconstitution of the lyophilized protein. The '856 patent defines a reconstitution stabilizer as any excipient that is capable of preventing aggregation upon reconstitution in an aqueous medium. The '856 patent further defines "excipient" by providing a long list of possible molecules that could be used in the invention at broad concentration ranges. Applicants contend that although the '856 patent includes KGF in a long list of proteins that can be used in the application and then further discloses KGF in specific formulations, the '856 patent neither teaches nor suggests a means to select the particular combination of molecules at the particular ranges claimed in the instant application. Moreover, the '856 patent does not provide any motivation or expectation of success to select the particular combination of molecules at the particular ranges claimed in the instant application. Thus, it would take more than mere optimization to arrive at the claimed invention.

Moreover, the '856 patent appears to actually teach away from the selection of the particular combination of molecules at the particular ranges encompassed by claimed invention by focusing on an isolated subset of excipients in combination with KGF. The '856 patent shows the effect of various osmolytes, water soluble polymers, surfactants, and lyotropic salts on aggregation in Table 1. Included in this list of molecules capable of reducing aggregation of KGF are molecules that are not encompassed by the instant invention. Thus the exclusion of the claimed elements of the invention from Table 1 can be taken as teaching away from selecting those elements in the instant invention.

In sum, HGS, Chen, and the '856 patent do not teach or suggest the claimed composition of polypeptide comprising the particular KGF-2 deletion mutant, a buffer, a diluent, and preservative in the claimed combination and in the claimed references. In particular, although Chen discloses the use of a KGF polypeptide in combination with specific buffers at specific combinations, this reference teaches away from the claimed invention. Similarly, the '856 patent teaches away from the claimed invention in that although it teaches an infinite number of combination of excipients, including ones encompassed by the instant claims, it focuses on a particular isolated subset of excipients

not envisioned by the instant invention. Thus, these references, either alone or in combination, fail to provide any motivation to combine the cited reference to arrive at the instant invention, nor do they provide any reasonable expectation of success. Accordingly, Applicants contend that the instant claims are not obvious of the references cited by the Examiner. On the basis of the arguments set forth above, Applicant respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-3, 5-17, 20-32, 36, 37, 71-73, 76, 80, 82-97, 100-115, 144-147, and 151-153 under 35 U.S.C. § 103 for obviousness.

***Conclusion***

Applicant respectfully requests that the above-made remarks and amendments be entered and made of record in the file history of the instant application. In view of the foregoing remarks, Applicant believes that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the allowance of this application. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: February 23, 2004

Respectfully submitted,

By _____

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